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CADAVEROUS PARTICLES AND INFECTION IN INJURED MAN*

Clinical Review based on the Semmelweis Lecture

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It is an honor to present the Semmelweis Lecture in this the 145th anniversary year of Semmelweis' institution of chlorine washings and the 131st anniversary year of the publication of his findings in Die Aetiologie der Begriff und die Prophylaxis des Kindbettfiebers (29). The 14 year hiatus, represented by those two anniversaries, can be viewed in the light of Semmelweis' tragic professional career as an early example of the maxim "publish or perish." I am particularly pleased to present this lecture because it gives me the opportunity to illustrate the applicability of Semmelweis' theories to other surgical infections and the importance of "cadaverous particles" in the pathogenesis of infections that occur in injured patients even today.

The changes that have occurred in the infections of burned patients, who serve as examples of extreme injury and show the same stereotypic, biphasic, multiorgan system responses as other injured patients (23), recapitulate the history of surgical infections (22). At the same time, those changes are premonitory of future epidemiologic changes in infections that will occur in other surgical patients. The "cadaverous particles" that have caused infection in burn wounds were, like those of Semmelweis, exogenous micro-organisms the importance of which was evident only when the disease was identified and characterized, its pathogenesis defined, and the effectiveness of specific prophylactic and therapeutic intervention was documented by improved survival.

The discovery of penicillin resulted in β-hemolytic streptococcal infections being superseded by staphylococcal infections as the most common cause of infection related mortality and morbidity in burned patients. In the late 1950's, when I first began to care for burns, the incidence of staphylococcal infections was already waning in the patients treated at our burn center. A clinical syndrome of wound degeneration, hypothermia, ileus, and leukopenia was seen with increasing frequency in patients with extensive burns particularly in children and the elderly (34). This syndrome, characterized by an inexorable downhill course refractory to antibiotic therapy, was associated with an almost universal mortality which was commonly diagnosed as "death due to burns." Studies at our center identified this disease as a consequence of systemic hematogenous dissemination of bacteria which had invaded tissue from an infected wound (33). The pathogenesis of gram-negative opportunistic invasive infections in burn patients was described almost a decade before "pseudomonas sepsis" became a common complication of other critically ill and severely injured patients (32).

The animal model developed to define the pathogenesis of invasive burn wound sepsis was also used to evaluate therapeutic interventions (35). The effectiveness of topical antimicrobial treatment was confirmed in that model and a topical agent was developed for clinical use (20). The use of topical antimicrobial agents effected a revolution in burn care and reduced the incidence of invasive Pseudomonas burn wound sepsis as a cause of death from 60% to 28% of fatal burns (28). At present, topical treatment has been refined to realize the advantages of both silver sulfadiazine and mafenide acetate burn creams by alternate application every 12 hours. The use of chlorhexidine gluconate in a surgical detergent solution for daily cleansing appears to reduce eschar maceration and is an important component of current topical chemotherapy. Such treatment limits microbial proliferation during the typically brief period between the time of injury and the time of surgical excision of the burned tissue.

The renaissance of surgical excision, which began in the early 1970's, has been so pervasive that all full-thickness burns of any magnitude and virtually all deep partial-thickness burns are excised and the wounds closed by autografting as soon as resuscitation is complete, usually within the first postburn week (18). The use of burn wound excision in combination with effective topical chemotherapy has further reduced the occurrence of invasive burn wound sepsis by promptly removing nonviable tissue. Those two

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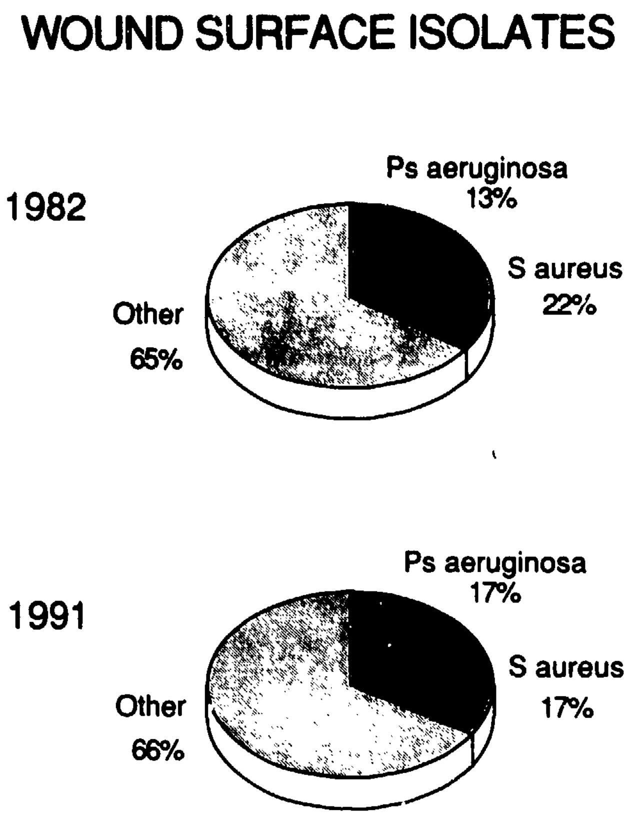

Fig. 1. Recovery of bacteria from surveillance cultures of the surface of burn wounds has not changed during the past decade.

factors have also changed the organisms causing burn wound infections. The incidence of invasive Pseudomonas burn wound infection has decreased, literally to the vanishing point, and coincident with that, recovery of Pseudomonas aeruginosa from the blood of our burn patients has become rare (15). The overall rate of colonization of burn wounds by Ps. aeruginosa has remained virtually unchanged but the time of colonization is much delayed (14) (Fig. 1). That delay may permit restoration of host defense mechanisms that prevent infection by such opportunistic organisms. Non-bacterial wound infections caused by organisms with lesser invasive potential have become relatively more common but they still represent only a fraction of the previously predominant gram-negative infections. During the last eight years, invasive burn wound infection was considered to be the primary cause of death in only 14 of the 221 burn patients who died at the U.S. Army Institute of Surgical Research. It should be noted that during that period an additional 24 patients developed invasive burn wound infections which were either controlled by operation prior to death or were an incidental finding at the time of autopsy. As an intimation of future infections in other surgical patients, 82% of those infections

Table I. *Incidence of invasive infection of burn wounds in 221 fatal burns, 1983–1990*

	Number (%) of patients
Invasive Infection the Primary Cause of Death	14 (6%)
Invasive Infection Present in the Burn Wound	38 (17%)*
Bacterial	8
Fungal	31

* One patient developed both bacterial and fungal infection.

were nonbacterial, usually caused by Aspergillus species (Table I).

In spite of the reduction in the incidence of invasive infection of burn wounds by Ps. aeruginosa, endemic pseudomonas strains and other gram-negative enteric organisms that were resistant to most antibiotics, were sporadically associated with "mini-epidemics" that were characterized by high mortality. (8, 26) Studies conducted by McManus et al., identified endemic pseudomonas strains with characteristic patterns of antibiotic resistance and verified that they were spread, just as in the days of Semmelweis, from patient to patient by attending personnel or by "free roaming" convalescent patients. Those investigators showed that "cohort" nursing of patients in individual rooms by assigned treatment teams, with emphasis on hand washing after every patient contact, use of impermeable aprons to prevent contamination of attire during wound care, and strict regulation of traffic to prohibit movement of staff and patients from the convalescent area to the critical care area successfully eliminated such strains from the environment (17). Since then resistant strains that were introduced sporadically by individual patients have been rapidly controlled by reinforcement of environmental control measures as soon as such organisms were identified.

The technological developments that permit continuous physiologic monitoring and effective support of organ systems have contributed to the increased survival of extensively burned patients and have also extended the survival time of those patients who ultimately die. The mean time to death of fatal burns has increased from 17 to 26 days over the past two decades. The longer survival of patients whose wounds remain open, either because of the extent of the burn or because of complications that require either long-term or repeated courses of broad spectrum antibiotics, places those patients at prolonged risk of infection and increases the likelihood that the organisms that cause the infections will be resistant

Table II. *Incidence of pneumonia and mortality of burn patients with pneumonia, 1985–90*

Year	Total number of patients	Number (%) that developed pneumonia	Number (%) that died
1985	190	40 (21)	29 (73)
1986	200	44 (22)	24 (55)
1987	208	33 (16)	16 (49)
1988	214	25 (12)	11 (44)
1989	209	32 (15)	11 (34)
1990	191	21 (11)	6 (29)

Table III. *Type of pneumonia in fatal burns 1962–90*
Figures are number (%).

	1962–1963	1967–1968	1983–1990
Number of patients with pneumonia	70	113	100
Type of infection:			
Airborne	23 (33)	74 (65)	90 (90)
Hematogenous	47 (67)	39 (35)	10 (10)*

* Candida ($n = 3$); aspergillus ($n = 2$).

bacteria, yeasts, or fungi (24). Those associations are illustrated by the findings that during the past eight years the mean time for a burn wound to become colonized by yeasts has been the 30th day after injury, the mean time to diagnosis of a candidal urinary tract infection the 48th day, and the mean time to diagnosis of candidal infections at other sites the 41st day.

The clinical impact of the wound infections that do occur has been lessened by daily wound surveillance and the liberal use of biopsy monitoring which facilitate histologic identification of invasive burn wound infection at an early stage of the disease when surgical and pharmacologic intervention can be carried out to control the infections before hematogenous dissemination can occur. The usefulness of histological examination of biopsy specimens and the applicability of such monitoring in the diagnosis and treatment of other surgical infections have been demonstrated by Stamenkovic and Lew (31). They reported that, by this method, the diagnosis of necrotizing fasciitis was made sooner and mortality was reduced. As noted previously, during the past eight years invasive burn wound infection was considered the cause of death in only 14 (6%) of the 221 fatal burns treated during that time, and the other 24 cases of burn wound infection that occurred in that cohort were either controlled surgically or thought to be incidental autopsy findings which were of little clinical moment.

Despite these improvements in wound care, infection remains the most common cause of morbidity and mortality in burn patients and the diminution of wound infection has exaggerated the relative importance of pneumonia (27). Pneumonia is not only the most common primary cause of death in fatal burns (45% of fatal burns in 1983–1990) but a common complication in all burn patients; the incidence has ranged from 11% to 22% over a recent six year period (Table II). The noted improvements in burn wound care have changed the predominant form of pneumonia presently encountered in burn patients. In the early 1960's, before the introduction of topical chemotherapy, two thirds of all pneumonias were caused by hematogenous spread of organisms from a remote focus of infection, usually an infected burn wound (25). In contrast, during the past eight years only 10% of pneumonias have been of hematogenous origin and 90% resulted from airborne infection (Table III).

Another factor that has contributed to the predominance of airborne infection as a cause of pneumonia is the increased number of patients with inhalation injury who are referred to burn centers in general and to our burn center in particular. The incidence of inhalation injury increases as burn size increases and 35.3% of our referral population, heavily weighted by patients with extensive burns, has concommitant inhalation injury (30). Technological advances, such as specially designed high frequency ventilators, have reduced the incidence of pneumonia from 46% to 26% in patients with endoscopically and radiographically confirmed inhalation injury and there has been a corresponding significant reduction in mortality (7). Even so, pneumonia continues to exert a significant co-morbid effect in burn patients with inhalation injury.

Another factor that is said to increase the risk of nosocomial pneumonia is the use of agents that neutralize acid or inhibit its production for prophylaxis against acute gastrointestinal stress ulcers (9). Unfortunately, the most commonly cited study that implicated such therapy was flawed by inappropriate pooling of patients. Preliminary results of a current prospective randomized study of 34 burn patients treated with antacids and an H2 histamine receptor antagonist and 33 patients treated with sucralfate show no difference in the incidence of nosocomial pneumonia or of mortality, and no difference in the rate of bacterial colonization of the stomach or upper airway.

The persistence of infection as the predominant co-morbid factor in injured humans has been attributed by some to intestinal translocation of bacteria as a consequence of impaired gastrointestinal blood flow

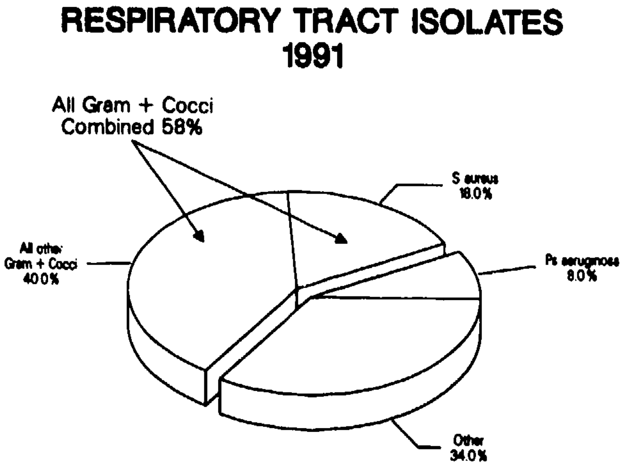

Fig. 2. Gram-positive cocci predominated in respiratory tract cultures from burned patients treated during 1991. Note that *S. aureus* was recovered more than twice as often as *Ps. aeruginosa*.

and the resulting alteration of mucosal permeability associated with hypovolemia. Studies at our Institute have shown that an increased lactulose: mannitol ratio (an index of increased gastrointestinal permeability) on the second day after the burn, correlated with the subsequent development of infection (11). Since the incidence of infection is related to the size of the burn, this finding may simply indicate an association rather than a cause and effect relationship, and further studies are underway to identify causality. If bacterial translocation was a significant etiologic factor in post-injury infection, one would anticipate a high incidence of anaerobic and gram-negative aerobic infections. However, among our burn patients such infections have in general decreased and gram-positive organisms have again become the predominant organisms causing infections as indicated by their prevalence in respiratory tract isolates (Fig. 2) and the current predominance of Staphylococcal pneumonia (27). This change in causative flora forewarns us of future infections in other special care units.

The change in predominant micro-organisms to a gram-positive flora appears to have contributed to a lessening in the impact of infection. The mortality enhancing effect of gram-negative bacteremia is not exerted by gram-positive bacteremia (12). It should be noted that the virulence of Staphylococcus aureus is strain-specific, as evidenced by episodes of unexplained profound physiologic instability that occurred after resuscitation in three burn patients that we recently treated. The strains of S. aureus recovered from those patients possessed the gene for the production of toxic shock syndrome toxin-1. Moreover, the endogenous "cadaverous particles" that have displaced the exogenous ones seem to be less dangerous. The mortality of those patients who still develop gram-negative bacteremia caused by their own micro-organisms is significantly less than that caused by the previously endemic infecting strains, which were eliminated by cohort nursing and the other environmental control measures noted above (16).

There are, in addition to microbial "cadaverous particles," non-microbial "cadaverous particles" in the sense that continued or excessive production of cytokines, enzymes, and other metabolic products of activated white cells can produce cadaveric changes in tissues and organs. Recent studies in our burn patients showed that circulating concentrations of interleukin-1-β (IL-1β) responded modestly to injury alone and showed little response to infection. Tumor necrosis factor-α (TNF-α) hardly responded to infection while IL-6 seemed to be a more sensitive indicator. These results question the cause and effect relationship between raised concentrations of circulating cytokines and injury and suggest that observed alterations in cytokine concentrations may be the effect rather than the cause of infection (10).

Other studies have documented alterations in both the function and size of various subpopulations of immune cells after burn injury and have attributed subsequent infections to such changes. Following an initial early reduction there is a rebound in the number of neutrophils but their response to a second stimulus is diminished (13, 21). Similarly, lymphocyte populations are altered in both number and function. The proportions of T lymphocytes and natural killer (NK) cells are greatly reduced compared to the B cell population (1). Within the T lymphocyte subpopulations the reduction in the proportion of CD8 positive cells is greater than that of CD4 positive cells which contradicts reports that the CD4:CD8 ratio was decreased (3). The correlation between the extent of the burn and the reduction in CD8 and CD4 populations indicates that the subpopulation changes were primary effects of the thermal injury and not a secondary response to treatment or to other pathophysiologic effects of thermal injury (4).

Expression of an adhesion receptor, the lymph node homing receptor, was lower in burned patients than in unburned controls and such changes in surface adherence molecules may be the mechanism that alters the distribution of lymphocyte populations among organs. The fact that the responses of the various cell populations varied independently of one another, and that changes in the NK population were positively rather than negatively related to the severity of the burn, suggests that the alterations in cellular subpopulations were differentially modulated by active processes (2).

The function of the various lymphocytic popu-

lations is also altered following thermal injury as indexed by differential responses to mitogens. The responses to the T cell specific mitogens concanavalin A and phytohemagglutinin were reduced in burned compared with control patients, but the response to pokeweed mitogen (which stimulates both B lymphocytes and T lymphocytes) was increased. Since burned patients have a higher proportion of B cells, the changes have been interpreted to mean that there is an increased number of B cells in each culture well rather than a change in the specific activity of the responding cells. Cultures of lymphocytes from burned patients also spontaneously incorporated more thymidine than did cultures of lymphocytes from control patients. The spontaneous production of immunoglobulin G (IgG) was also increased in lymphocytes cultured from burned patients compared with that in lymphocytes cultured from controls, but IgM production was unchanged in lymphocytes cultured from burned patients. Stimulated production of IgG by lymphocytes from burned patients was comparable to that of control cells but stimulated concentrations of IgM were lower than in control cells. It is worth noting that intravenous administration of hyperimmune gamma globulin had a measureable effect on the immune system and decreased the proportion of B lymphocytes in treated patients compared to untreated patients, an effect considered to represent a feedback control mechanism (1).

Infection appears to cause additional alterations in circulating populations of lymphocytes. A decrease in the proportion of CD8 positive cells and a reduced response to mitogens have been correlated with the onset of infection. A system that tests lymphocyte function by measuring individual cell proliferation has allowed assessment of the proliferative capacity of each subpopulation of lymphocytes in terms of the presence of IL-2 receptors. Freshly isolated lymphocytes from burned patients showed a twofold increase in the expression of IL-2 receptors, 10% compared with a control value of 5%. After culture for 24 hours with concanavalin A, expression of IL-2 receptor was evident on only about half as many CD4 and CD8 positive cells from burned patients as from unburned controls, even though the proportions of NK cells and B lymphocytes that expressed such receptors did not differ from those of the controls (5). In short, B cell lymphocyte function seems relatively intact after a burn injury whereas both the number and function of T cells are suppressed.

Many of the immunologic changes observed in burned patients appear to represent the effects of infection rather than causes. As such, they assume the character of agents of "cadaverous particles" rather than being "cadaverous particles" in their own right. Even so, various immunomodulators have been evaluated by many investigators. In patients studied at our burn center granulocyte-macrophage colony stimulating factor (GM-CSF) increased leukocyte counts by 50% and restored the ability of the neutrophils to produce superoxide (6). Although the latter effect has been postulated by some to be potentially deleterious, it might equally well be beneficial if the superoxide radical acted as an annihilator of nitric oxide rather than as a cytotoxic ion. Other immunomodulators have seemed to be effective in laboratory studies but their clinical applications are uncertain because of species specificity; sensitivity to the intervals between injury, treatment, and infectious challenge; and the narrow therapeutic margin of many of the agents used. Agents such as intravenous gamma globulin (IGIV) that have been evaluated clinically have had no consistent effect on the occurrence of infection or improvement in survival (19).

In summary, topical chemotherapy, techniques of surgery, technological developments, tactics in nursing care, time related epidemiologic changes, and therapeutic agents that have enhanced immune competence, have brought about improved but still imperfect survival of burned and other injured patients. Those six factors have reduced the incidence of invasive burn wound sepsis, altered the predominant flora of the burn wound and of other infections; eliminated endemic virulent strains, and protected against the introduction of new epidemic strains; altered the predominant form of pneumonia; extended survival time; and improved burn patient salvage even though nonbacterial organisms have become the predominant cause of invasive infections and staphylococci have become the overall predominant causative organisms of infections in burned patients. The improvement in survival that has resulted from early identification and control of modern day "cadaverous particles" has been greatest in those burned patients who, because of the extent of their injury or the presence of associated conditions, are treated in burn centers. In that setting, the multidisciplinary care required by severely burned patients can be provided, life threatening complications can be identified, and clinical problems subjected to sophisticated investigation. Further improvement in the survival of badly injured patients is anticipated as the work begun 145 years ago by Ignaz Philipp Semmelweis is continued, and the "cadaverous particles" responsible for the continually evolving infectious complications of injured patients are brought under control.

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